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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

:

Hashime KANAZAWA et al.

:

**Mail Stop: ACCOUNTING DIVISION
REFUND BRANCH**

Serial No. 10/533,806

:

Filed May 5, 2005

:

**Attorney Docket No. 2005_0741A
Confirmation No. 8202**

PYRAZOLONAPHTHYRIDINE DERIVATIVES

**[Corresponding to PCT/JP2003/014119
Filed November 6, 2002]**

REQUEST FOR REFUND

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

Sir:

Applicants respectfully request a refund of charges totaling \$760.00 posted to Deposit Account No. 23-0975 on August 19, 2005. The corresponding fee code indicates the charges are for a national stage search fee and multiple dependent claims, respectively. Applicants assert the charges are incorrect.

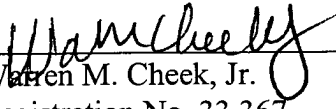
The \$400.00 National Stage Search fee was paid by check no. 68100 on May 5, 2005 at the time of filing. A copy of the PTO date-stamped postcard and cancelled check are enclosed as evidence of prior payment. The \$360.00 charge for multiple dependencies is incorrect because they were removed in the Preliminary Amendment, also filed on May 5th. A copy of the Amendment is enclosed for reference.

Both charges are the result of PTO oversight and we kindly request a refund totaling \$760.00 to the deposit account of undersigned, no. 23-0975. If there are any questions regarding

this matter, please contact Kara Reade, Accounting Assistant, at (202) 721-8226.

Respectfully submitted,

Hashime KANAZAWA et al.

By 
Warren M. Cheek, Jr.
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January 13, 2006

2005_0741A

ATTY DOCKET #: 2005_0741A

Due Date: May 6, 2005

OUR REF: 2005_0741A/WMC/01332

Applicant: Hashime KANAZAWA et al.

Serial No.: NEW

Filing Date: May 5, 2005

Title: PYRAZOLONAPHTHYRIDINE DERIVATIVES

10/533806

Receipt of the following papers is acknowledged:

1. Transmittal Letter to the United States Designated/Elected Office (DO/EO/US) Concerning a Filing Under 35 USC 371 (National stage application of PCT/JP2003/014119)
2. Attachments: Verification of Translation (A) An International Application including Specification, Claims and Abstract (103 pages), (B) Executed Declaration, (C) IDS, PTO-1449 form with 9 references, International Search Report, (D) Assignment Recordal Sheet, Assignment, (E) Preliminary Amendment, (F) WO 2004/041819.
3. Check in the amount of \$1,390.00

THE COMMISSIONER IS AUTHORIZED
TO CHARGE ANY DEFICIENCY IN THE
FEE FOR THE PAPER TO DEPOSIT
ACCOUNT NO. 23-0575.

Date May 5, 2005

Attorney WMC/dlk

[Check No. 68100]

JC07 Rec'd PCT/PTO 0 5 MAY 2005

68100

WENDEROTH, LIND & PONACK, L.L.P.
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PAY TO THE ORDER OF THE COMMISSIONER OF PATENTS AND TRADEMARKS

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DOLLARS

KANAZAWA	NEW 1332	New PCT Appl.	2005_0741A WMC	1,150.00
KANAZAWA	NEW 1332	Claims extra total over 2	2005_0741A WMC	200.00
KANAZAWA	NEW 1332	Assignment Recordation	2005_0741A WMC	40.00
MEMO				

Michael R. Davis
AUTHORIZED SIGNATURE

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PATENT AND TRADEMARK OFFICE
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of : **Mail Stop: PCT**
Hashime KANAZAWA et al. : Docket No. 2005_0741A
Serial No. NEW :
Filed May 5, 2005 :

PYRAZOLONAPHTHYRIDINE DERIVATIVES
[Corresponding to PCT/JP2003/014119
Filed November 5, 2003]

PRELIMINARY AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

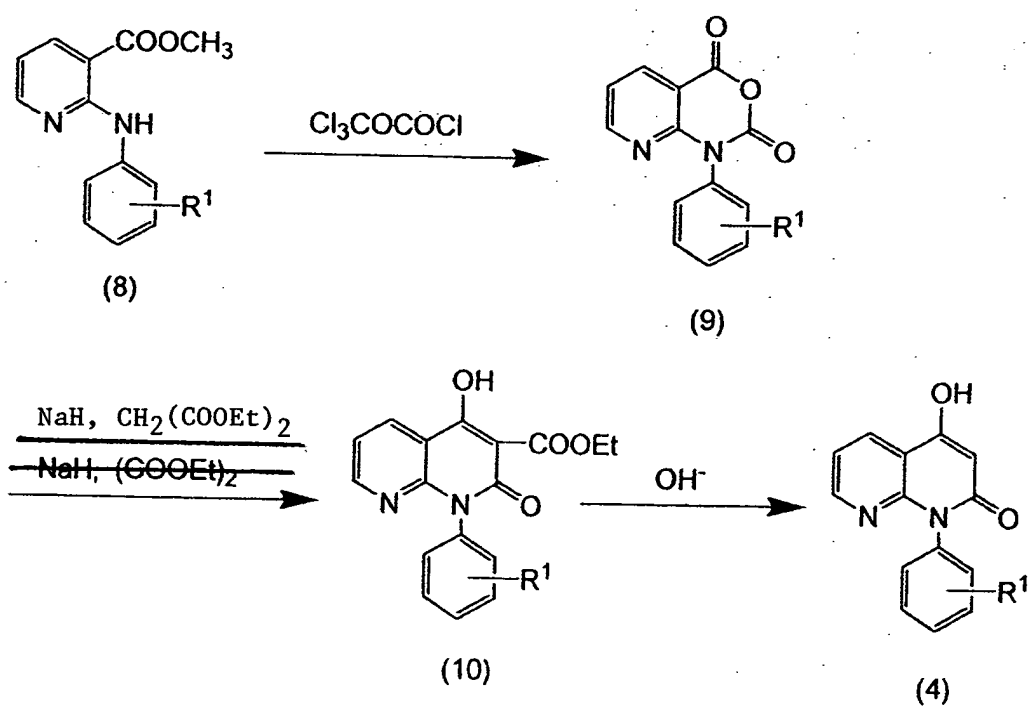
Prior to calculating the filing fee, please amend the above-identified application
as follows:

AMENDMENTS TO THE SPECIFICATION

Page 1, immediately after the title, please insert:

This application is a U.S. national stage of International Application No.
PCT/JP2003/014119 filed November 5, 2003.

Page 23, please replace the formula with the following rewritten formula:



Scheme (IV)

Page 36, lines 17-26, please rewrite as follows:

After airway pressure became stable, an ovalbumin solution (1 mg/ml, dissolved in physiological saline) was administered at a dose of 1 ml/kg via a tube with which the right jugular vein of guinea pigs was cannulated. Each area under airway pressure-time curve (AUC) was obtained by measuring amplitudes of the airway pressure prior to the antigen-challenge, 1, 2, 3, 4, 5, ~~11~~, 10, 15 and 20 minutes post-challenge, and each percent increase (%) in airway resistance was further calculated according to the following equation:

Page 41, line 20 to page 42, line 2, please rewrite as follows:

The Compound of the present invention (Example No. 9) was administered orally to ICR mice (~~7~~ 5 animals per group) as a test compound. During one week, the mice were observed for the time course of their general health conditions and measured for their body weight. The test compound was suspended in 0.5% CMC-Na solution and given orally to the animal at a dose of 100 or 300 mg/10 ml/kg in a forced manner.

Page 46, lines 8-19, please rewrite as follows:

(1) To methyl 2-(3-nitrophenylamino)nicotinate (5.00g, 18.3mmol; synthesized according to WO, A, 01/42244) was added 1,2-dichloroethane (90ml), and the mixture was heated at 80°C to form a solution. To the resultant solution was added trichloromethyl chloroformate (also called: diphosgene, 6.7ml, 54.9mmol) gradually dropwise over about 30 minutes. Three hours later, the mixture was admixed with activated carbon (150mg), heated under reflux for 30 minutes, filtered, then evaporated, and dried under reduced pressure to give a mixture (5.32g, quantitative) containing 1-(3-nitrophenyl)-2H-pyrido[2,3-d][3,4-1,3]oxazin-2,4(1H)-dione as crystals.

Page 46, line 27 to page 47, line 11, please rewrite as follows:

(2) To a solution of diethyl malonate (2.99g, 18.7mmol) in dimethylacetamide (28ml) was added sodium hydride (about 60%, 933mg, 23.3mmol) with ice-cooling, and the mixture was stirred to form a solution until the production of hydrogen was completed. After the resultant solution was added to a mixture (5.32g) containing 1-(3-

nitrophenyl)-2H-pyrido[2,3-d][~~3,4~~ 1,3]oxazin-2,4(1H)-dione with ice-cooling, the mixture was stirred for 3 hours at 150°C, cooled to room temperature, then treated with ethyl acetate, and allowed to stand. The resulting precipitate was filtered off, and washed with ethyl acetate. The residue obtained after filtration was dissolved in water, acidified to pH1 with hydrochloric acid to form precipitates which were filtered off, washed with water, and dried to give 3-ethoxycarbonyl-4-hydroxy-1-(3-nitrophenyl)-1,8-naphthyridin-2(1H)-one (4.42g, yield for 2 steps from (1): 66%) as crystals.

Page 61, lines 14-24, please rewrite as follows:

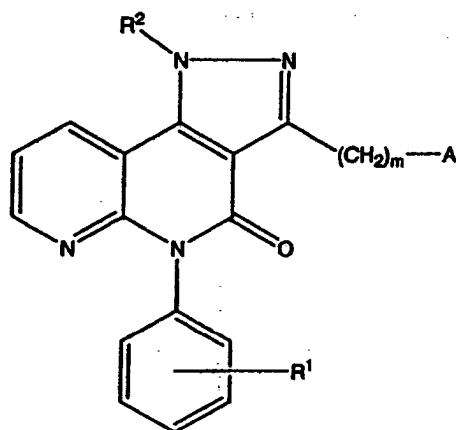
(1) To a solution of methyl 2-(3-fluorophenylamino)-nicotinate (4.90g, 16.2mmol; synthesized according to WO, A, 01/42244) in 1,2-dichloroethane (80ml) was added at 80°C trichloromethyl chloroformate (also called: diphosgene, 5.9ml, 48.3mmol) gradually dropwise over about 30 minutes. Three hours later, activated carbon (130mg) was added, and the mixture was heated under reflux for 30 minutes, filtered off, and then evaporated. The resultant residue was washed with isopropyl ether, and dried to give 1-(3-fluorophenyl)-2H-pyrido[2,3-d][~~3,4~~ 1,3]oxazin-2,4(1H)-dione(3.42g, 82%) as crystals.

Page 62, lines 1-16, please rewrite as follows:

(2) To a solution of diethyl malonate (1.50g, 9.30mmol) in dimethylacetamide (14ml) was added sodium hydride (about 60%, 467mg, 11.65mmol), and the mixture was stirred to form a solution until the production of hydrogen was completed. To the resulting solution was added 1-(3-fluorophenyl)-2H-pyrido[2,3-d][~~3,4~~ 1,3]oxazin-2,4(1H)-dione (2.36g, 9.15mmol) while ice-cooling, and the mixture was stirred at 150°C for 1 hour, cooled to room temperature, treated with ethyl acetate, allowed to stand. The resultant precipitate was collected by filtration, and washed with ethyl acetate, filtered off to give a residue which was dissolved in water, acidified to pH1 with hydrochloric acid to form precipitates. The resultant precipitate was collected by filtration, washed with water, and dried to afford 3-ethoxycarbonyl-1-(3-fluorophenyl)-4-hydroxy-1,8-naphthyridin-2(1H)(2.66g, 88%) as crystals.

AMENDMENTS TO THE CLAIMS

1. (Original) A compound of the formula (1):



(1)

wherein:

A is phenyl, pyridyl, 1-oxypyridyl, or thienyl, which may be unsubstituted or optionally substituted with one or more members selected from the group consisting of hydroxyl, halogen, cyano, nitro, lower alkyl, lower alkoxy, lower alkylcarbonyloxy, amino, carboxyl, lower alkoxycarbonyl, carboxy-lower alkylene, lower alkoxycarbonyl-lower alkylene, lower alkylsulfonyl, lower alkylsulfonylamino, and ureido;

R¹ is a group selected from the group consisting of hydrogen, hydroxyl, halogen, cyano, nitro, lower alkoxy, amino, carboxyl, and lower alkoxycarbonyl;

R² is hydrogen or lower alkyl; and

m is an integer of 1 to 3;

or a pharmaceutically acceptable salt thereof.

2. (Original) The compound according to Claim 1, wherein A is phenyl; or a pharmaceutically acceptable salt thereof.

3. (Original) The compound according to Claim 1, wherein A is pyridyl or 1-oxypyridyl; or a pharmaceutically acceptable salt thereof.

4. (Original) A compound, or a pharmaceutically acceptable salt thereof, which is selected from the group consisting of

3-benzyl-5-phenyl-1H-pyrazolo[4,3-c][1,8]-naphthyridin-4(5H)-one,

5-phenyl-3-[2-(1-oxypyridin-4-yl)ethyl]-1H-pyrazolo[4,3-c][1,8]-naphthyridin-4(5H)-one,

5-(3-nitrophenyl)-3-[2-(pyridin-4-yl)ethyl]-1H-pyrazolo[4,3-c][1,8]-naphthyridin-4(5H)-one,

3-(4-fluorobenzyl)-5-phenyl-1H-pyrazolo[4,3-c][1,8]-naphthyridin-4(5H)-one,

3-(4-carboxymethylbenzyl)-5-phenyl-1H-pyrazolo[4,3-c][1,8]-naphthyridin-4(5H)-one,

3-(2-methoxybenzyl)-5-phenyl-1H-pyrazolo[4,3-c][1,8]-naphthyridin-4(5H)-one,

3-(2-nitrobenzyl)-5-phenyl-1H-pyrazolo[4,3-c][1,8]-naphthyridin-4(5H)-one,

3-(2,5-dimethoxybenzyl)-5-phenyl-1H-pyrazolo[4,3-c][1,8]-naphthyridin-4(5H)-one,

3-(4-ethoxycarbonylmethylbenzyl)-5-phenyl-1H-pyrazolo[4,3-c][1,8]-naphthyridin-4(5H)-one,

3-benzyl-5-(3-cyanophenyl)-1H-pyrazolo[4,3-c][1,8]-naphthyridin-4(5H)-one,

3-benzyl-5-(3-nitrophenyl)-1H-pyrazolo[4,3-c][1,8]-naphthyridin-4(5H)-one and

3-benzyl-5-(3-fluorophenyl)-1H-pyrazolo[4,3-c][1,8]-naphthyridin-4(5H)-one.

5. (Currently amended) A pharmaceutical composition which comprises an effective amount of a compound according to ~~any of Claims 1 to 4~~ Claim 1, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable carrier.

6. (Currently amended) A phosphodiesterase IV inhibitor comprising an effective amount of a compound according to ~~any of Claims 1 to 4~~ Claim 1, or a pharmaceutically acceptable salt thereof.

7. **(Currently amended)** A drug for the prophylaxis and/or treatment of at least one member selected from diseases or abnormal conditions directly or indirectly related to phosphodiesterase IV, said drug comprising an effective amount of a compound according to ~~any of Claims 1 to 4~~ Claim 1, or a pharmaceutically acceptable salt thereof.
8. **(Currently amended)** A drug comprising an effective amount of a compound according to ~~any of Claims 1 to 4~~ Claim 1, or a pharmaceutically acceptable salt thereof, said drug for preventing and/or treating at least one respiratory disease selected from the group consisting of:
- bronchial asthma including chronic bronchial asthma and atopic asthma;
 - acute bronchitis; chronic bronchitis; asthmatic bronchitis; pneumonic diseases; pulmonary emphysema; chronic obstructive pulmonary disease (COPD); and acute respiratory distress syndrome (ARDS).
9. **(Currently amended)** An anti-asthmatic comprising an effective amount of a compound according to ~~any of Claims 1 to 4~~ Claim 1, or a pharmaceutically acceptable salt thereof.
10. **(New)** A pharmaceutical composition which comprises an effective amount of a compound according to Claim 2, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable carrier.
11. **(New)** A pharmaceutical composition which comprises an effective amount of a compound according to Claim 3, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable carrier.
12. **(New)** A pharmaceutical composition which comprises an effective amount of a compound according to Claim 4, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable carrier.

- 13. (New)** A phosphodiesterase IV inhibitor comprising an effective amount of a compound according to Claim 2, or a pharmaceutically acceptable salt thereof.
- 14. (New)** A phosphodiesterase IV inhibitor comprising an effective amount of a compound according to Claim 3, or a pharmaceutically acceptable salt thereof.
- 15. (New)** A phosphodiesterase IV inhibitor comprising an effective amount of a compound according to Claim 4, or a pharmaceutically acceptable salt thereof.
- 16. (New)** A drug for the prophylaxis and/or treatment of at least one member selected from diseases or abnormal conditions directly or indirectly related to phosphodiesterase IV, said drug comprising an effective amount of a compound according to Claim 2, or a pharmaceutically acceptable salt thereof.
- 17. (New)** A drug for the prophylaxis and/or treatment of at least one member selected from diseases or abnormal conditions directly or indirectly related to phosphodiesterase IV, said drug comprising an effective amount of a compound according to Claim 3, or a pharmaceutically acceptable salt thereof.
- 18. (New)** A drug for the prophylaxis and/or treatment of at least one member selected from diseases or abnormal conditions directly or indirectly related to phosphodiesterase IV, said drug comprising an effective amount of a compound according to Claim 4, or a pharmaceutically acceptable salt thereof.
- 19. (New)** A drug comprising an effective amount of a compound according to Claim 2, or a pharmaceutically acceptable salt thereof,
said drug for preventing and/or treating at least one respiratory disease selected from the group consisting of:
bronchial asthma including chronic bronchial asthma and atopic asthma;
acute bronchitis; chronic bronchitis; asthmatic bronchitis; pneumonic

diseases; pulmonary emphysema; chronic obstructive pulmonary disease (COPD); and acute respiratory distress syndrome (ARDS).

20. (New) A drug comprising an effective amount of a compound according to Claim 3, or a pharmaceutically acceptable salt thereof,

said drug for preventing and/or treating at least one respiratory disease selected from the group consisting of:

bronchial asthma including chronic bronchial asthma and atopic asthma; acute bronchitis; chronic bronchitis; asthmatic bronchitis; pneumonic diseases; pulmonary emphysema; chronic obstructive pulmonary disease (COPD); and acute respiratory distress syndrome (ARDS).

21. (New) A drug comprising an effective amount of a compound according to Claim 4, or a pharmaceutically acceptable salt thereof,

said drug for preventing and/or treating at least one respiratory disease selected from the group consisting of:

bronchial asthma including chronic bronchial asthma and atopic asthma; acute bronchitis; chronic bronchitis; asthmatic bronchitis; pneumonic diseases; pulmonary emphysema; chronic obstructive pulmonary disease (COPD); and acute respiratory distress syndrome (ARDS).

22. (New) An anti-asthmatic comprising an effective amount of a compound according to Claim 2, or a pharmaceutically acceptable salt thereof.

23. (New) An anti-asthmatic comprising an effective amount of a compound according to Claim 3, or a pharmaceutically acceptable salt thereof.

24. (New) An anti-asthmatic comprising an effective amount of a compound according to Claim 4, or a pharmaceutically acceptable salt thereof.

REMARKS


The specification has been amended to reflect the national stage status, as well as to correct minor typographical errors in the specification which are self-explanatory.

The claims have been amended to remove the multiple dependencies to reduce the PTO filing fee.

Favorable action on the merits is solicited.

Respectfully submitted,

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